ATTENUATION BIOMARKERS OF DENGUE 4 VIRUS STRAIN 1036 PDK40 INFECTIOUS CLONE

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Abstract. Dengue viruses (DENV) transmitted by *Aedes* mosquitoes cause hemorrhagic fever and shock syndrome in tropical and subtropical regions. Live-attenuated (LAV) DEN4V 1036 PDK40 showed small plaque size in LLC-MK2 cells at 37ºC, but not at 39.4ºC and produced low neurovirulence in suckling mice. The major limitations of LAV are genetic instability and reversion. In order to expand the tools available for dengue vaccine development, an infectious clone (IC) DEN4V 1036 PDK40 was constructed from LAV DEN4V 1036 PDK40. IC-DEN4V-1036-PDK40 demonstrated attenuated characteristics, namely, small/pinpoint plaque sizes, temperature sensitivity, low growth efficiency in *Ae. aegypti*, and low neurovirulence in suckling mice. These results indicate IC-DEN4V-1036-PDK40 fulfilled all *in vitro* and *in vivo* safety requirements and should be useful for development as a dengue or a backbone for *Flavivirus*-chimeric vaccines.

Keywords: dengue, vaccine, dengue virus, Gibson assembly, infectious clone, live attenuated vaccine

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